Received: 19 January 2024 | Revised: 13 August 2024 | Accepted: 3 September 2024

DOI: 10.1002/hsr2.70079

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

The prevalence of hepatitis C virus genotypes and factors associated with cirrhosis, fatty liver, and viral load: A registry-based cross-sectional cohort study in Western Iran during 1999–2023

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Funding information

Vice Chancellery for Research and Technology, Kermanshah University of Medical Sciences, Grant/Award Number: 4030195

Abstract

Background and Aims: Hepatitis C virus (HCV) is an important infectious disease that imposes a significant burden on healthcare systems. Determining the prevalence of HCV genotypes in a area is essential for the successful implementation of HCV elimination programs and allocation of financial resources to direct-acting antiviral direct-acting antivirals (DAA) treatments against prevalent HCV genotypes. Accordingly, we conducted a registry-based cross-sectional cohort study to investigate the prevalence of HCV genotypes and factors associated with cirrhosis, fatty liver, and viral load in Kermanshah Province, Western Iran.

Methods: Patients presenting to the Hepatitis Clinic of the Research Center for Infectious Diseases affiliated with Kermanshah University of Medical Sciences between 1999 and 2023 were enrolled in this study. Serum samples were collected to assess HCV genotypes and viral load. Additionally, demographic data and the status of cirrhosis and fatty liver were extracted from the registry system records throughout the study period.

Results: Records of 828 patients with an average age of 40.38 ± 11.72 years (range: 11–80 years) were included in the study that 721 individuals were male, and 107 were female. The prevalence of fatty liver and cirrhosis was 30.3% and 12.9%, respectively. Four genotypes (1, 2, 3, and 4) and four subtypes (1a, 1b, 3a, and 3b) were identified, with subtype 3a (55.7%) being the most prevalent, followed by subtype 1a (34.3%). None of the variables including age, gender, viral load level, and genotypes 1 and 3 were associated with fatty liver or cirrhosis. However, age, gender, and genotype were correlated with the viral load ($p \leq 0.05$).

Conclusion: The most common HCV subtypes in Kermanshah were 3a and 1a. Genotypes 2 and 4 were identified in one case each. Further studies on identifying

HCV subtypes in different regions of the country are recommended to manage HCV infection and predict the prognosis.

KEYWORDS
cirrhosis, fatty liver, genotype, HCV, Iran, Kermanshah

1 | INTRODUCTION

Hepatitis C virus (HCV) infection poses significant global challenges.[1] The World Health Organization (WHO) predicts that approximately 71 million people worldwide are chronically infected with HCV,[2] leading to 399,000 deaths annually due to complications from this disease.[3] HCV infection can manifest in both acute and chronic forms, with nearly 70% of cases progressing towards chronicity.[4] This disease is primarily transmitted through blood contact[4] and is a major contributor to conditions such as cirrhosis, liver failure, and liver cancer.[1,5]

HCV is a positive-sense, single-stranded RNA virus with a polyprotein structure. This virus, which belongs to the flaviviridae family,[6] exhibits a high degree of sequence diversity within its nine genomes. Due to the extensive nucleotide sequence variability across the HCV genome, the virus is classified into eight major genotypes[7,8] and 93 subtypes[8,9] with at least 30% nucleotide sequence divergence. The genotypes 1, 2, and 3 are prevalent genotypes worldwide.[10,11] The distribution of these genotypes is largely geographically dependent.[11,12] Genotypes 1 and 2 are mainly found in the western regions, genotype 3 in South Asia, and genotypes[13] 4, 5, and 6 in the Middle East,[13] Central Africa, Southern Africa, and Southeast Asia, respectively.[14] Genetic diversity in HCV influences disease progression and treatment response in infected individuals.[14] In some studies, infection with Genotype 3 has been associated with a greater likelihood of progressing to cirrhosis compared to other genotypes. Furthermore, the rate of progression to cirrhosis has been higher in Genotype 3.[15] According to available evidence from eight meta-analyses, the rate of progression to fibrosis in patients with Genotype 3 HCV infection is 50% higher compared to patients with other genotypes.[16] Genotypes 1b and 1a demonstrated weaker responses to older treatments based on interferon and ribavirin, respectively, while Genotypes 3a and 3b exhibited the best response. However, for newer treatments based on direct-acting antiviral directly acting antivirals (DAA) drugs, Ggenotype 1 tends to respond better than Genotype 3. In fact, the HCV genotype and subtype are crucial variables in selecting the appropriate type of medication and determining the treatment duration.[17,18] Also, resistance-associated substitutions (RAS) in HCV that occur as specific mutations in the NS3 protease, NS5A and NS5B polymerase regions of the HCV genome have been associated with resistance to certain DAAs. This prevalence of RAS, which varies among different HCV genotypes and subtypes, can develop during DAA therapy and is associated with reduced susceptibility to certain antiviral drugs. The presence of RAS can affect treatment results and lead to treatment failure or relapse.[19,20] Therefore, diagnosing the infecting virus accurately and determining its genotype hold significant importance for HCV treatment planning.

In Iran, the prevalence of HCV is around 0.13% among blood donors and less than 1% in the general population,[21] with higher rates reported in western provinces such as Kermanshah.[22] According to a study conducted in 2016 in Kermanshah province, the prevalence of Hepatitis C was 0.85% in the general population. This province has a higher number of drug addicts compared to neighboring provinces, and the shared use of syringes among injection drug users is one of the main risk factors for HCV transmission in Iran.[22] In recent years, the number of injection drug users has increased in Iran, especially in Kermanshah[23] which can lead to an increase in HCV cases. However, there is no comprehensive study of the prevalence of HCV genotypes in Kermanshah, Iran. Therefore, the purpose of the present study was to provide a general overview of the distribution of Hepatitis C genotypes and to determine the predominant genotype and factors associated with cirrhosis, fatty liver, and viral load in the studied community.

2 | MATERIALS AND METHODS

2.1 | Study design and population

All patients who presented to the Hepatitis Clinic of the Research Center for Infectious Diseases affiliated with Kermanshah University of Medical Sciences between 1999 and 2023 were included in this cross-sectional descriptive-analytical study. The data of the patients with a diagnosis of chronic HCV infection were entered into the chronic hepatitis registry system established at this center.

Demographic data, HCV genotypes, cirrhosis and fatty liver status, and viral load, were extracted from the patients' electronic records available in the registry system during the study period. The liver disease was staged based on clinical evidence of cirrhosis determined by a physician and the Ishak fibrosis score recorded after liver biopsy. Fibroscan scores were not recorded. The diagnosis of nonalcoholic fatty liver disease (NAFLD) was established based on clinical evidence, liver enzymes, and ultrasound criteria. Patients with alcoholic fatty liver, incomplete records, or missing HCV genotype tests, as well as repeated cases based on their name, national ID, and gender were excluded from the study.

2.2 | Laboratory methodology

The diagnosis of chronic HCV infection was based on the presence of anti-HCV antibody and HCV RNA. To diagnose chronic HCV infection, blood samples (8 mL) were collected from participants in ethylenediaminetetraacetic acid tubes. After plasma separation, anti-HCV antibody was

measured in serum samples using an enzyme-linked immunosorbent assay (ELISA) test (PishtazTeb). Subsequently, the seropositive samples were evaluated for the identification of HCV RNA (rt–RT-PCR primer/probe kit (Path-HCV-standard kit, genesig® kits; Primerdesign Ltd), viral load measurement, and genotype determination. Genotyping was performed using a commercial kit (AmpliSens® HCV-genotype-FRT PCR kit; InterLabService 20/13, b.2). This kit is designed for qualitative detection and differentiation of HCV genotypes 1a, 1b, 2, 3a, 4, and 5a.

2.3 | Statistical analysis

Analysis was done using STATA software (version 14.2, SPSS Inc.) at 95% confidence level. The mean (standard deviation) and frequency (percentage) were used for quantitative and qualitative variables, respectively. Comparison of viral load based on demographic and clinical characteristics was done by Mann–Whitney *U* and Kruskal–Wallis test. Bivariate logistic regression analysis was performed for reporting crude odds ratios (OR) with a 95% confidence interval (95% CI). All the statistical analyses were done using two-tailed tests. The $p \leq 0.05$ was considered significant.

3 | RESULTS

During the study period, a total of 884 patients diagnosed with HCV were identified at the Hepatitis Clinic of Kermanshah University of Medical Sciences. Out of this number, 10 cases were excluded due to data duplication, and 46 cases were excluded due to missing data in their records. The characteristics of the participants are presented in Table 1. In total, 828 patient records with a mean age of 40.38 ± 11.72 years (range: 11–80 years) were included in the study. The majority of patients were below 39 years (51.7%). Among them, 721 (87.1%) were male and 107 (12.9%) were female. Low viral load levels (≤800,000 IU/mL) were recorded in 357 patients (43.1%), while high viral load levels (>800,000 IU/mL) were observed in 422 patients (51%). Cirrhosis and fatty liver were observed in 12.9% and 30.3% of the patients, respectively. Viral load data were unavailable for 49 patients, and data regarding cirrhosis was unavailable for seven patients.

In this study, four genotypes (1, 2, 3, and 4) and four subtypes (1a, 1b, 3a, and 3b) were identified. As depicted in Figure 1, subtype 3a (55.7%) was the most prevalent, followed by subtype 1a (34.3%). Genotypes 2 and 4 were each reported in only one patient. Mixed infection was observed in 0.8% of the patients. Additionally, the HCV genotype was unidentifiable in 22 (2.7%) patients.

To assess the association between cirrhosis or fatty liver and HCV infection genotypes, Genotypes 2 and 4 were excluded due to the very low number of infected patients. It was found that fatty liver or cirrhosis had no significant relationship with age, gender, genotype, and viral load (Tables 2 and 3). In Genotype 1, the likelihood of fatty liver was 26% lower, the likelihood of cirrhosis was 26% higher, and the likelihood of high viral load was 32% higher compared to Genotype 3. However, these differences were not statistically significant ($p > 0.05$). Age groups, gender, and genotype had a significant correlation with the viral load median value (Table 4).

TABLE 1 Demographic and clinical characteristics of participants.

Variable	Total number (%)
Gender, *N* (%)	
Male	721 (87.1)
Female	107 (12.9)
Age group (years), *N* (%)	
≤39	428 (51.7)
40–59	347 (41.9)
≥60	53 (6.4)
HCV viral load log $_{10}$, (IU/mL), *N* (%)*	
Low (≤800,000 IU/mL)	357 (43.1)
High (>800,000 IU/mL)	422 (51)
Cirrhosis, *N* (%)**	
Yes	107 (12.9)
No	714 (86.2)
Fatty liver, *N* (%)	
Yes	251 (30.3)
No	577 (69.7)

Abbreviation: HCV, hepatitis C virus.
*Viral load data were unavailable for 49 patients.
**Data regarding cirrhosis assessment were unavailable for seven patients.

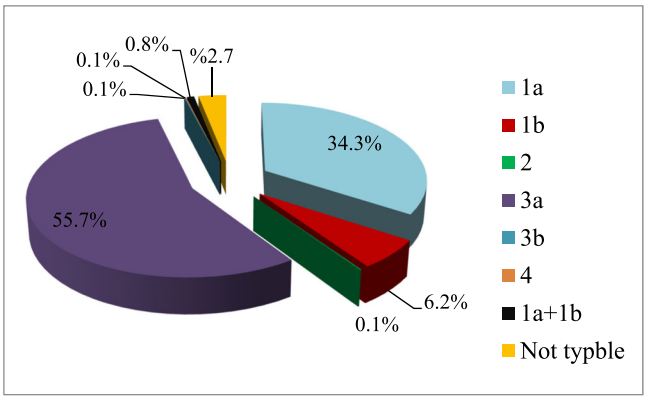

FIGURE 1 Distribution of hepatitis C virus genotypes and their subtypes.

4 | DISCUSSION

Hepatitis C is a major global public health concern.[3] The prevalence of hepatitis C varies from 0.2% to 40% in different countries across the world. In Iran, the estimated prevalence of HCV is between less

TABLE 2 Variables related to fatty liver in patients with chronic HCV infection, logistic regression model results.

Variable	Total number (%)	Patients with fatty liver, *N* (%)	OR (95% CI)	*p*-Value
Age			0.9 (0.70–1.11)	0.42
Sex				
Male	721 (87.1)	217 (86.45)	Ref.	0.73
Female	107 (12.9)	34 (13.54)	1.079 (0.69–1.67)	
Genotype				
3	459 (55.4)	153 (33.3)	Ref.	0.056
1	344 (41.5)	93 (27)	0.74 (0.55–1.01)	
Viral load				
$<8 \times 10^5$	357 (43.1)	109 (43.42)	Ref.	0.64
$\geq 8 \times 10^5$	422 (51)	135 (53.78)	1.07 (0.79–1.45)	

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.

TABLE 3 Variables related to cirrhosis in patients with chronic HCV infection, logistic regression model results.

Variable	Total number (%)	Patients with cirrhosis, *N* (%)	OR (95% CI)	*p*-Value
Age			0.7 (0.55–1.10)	0.16
Sex				
Male	721 (87.1)	94 (87.85)	Ref.	0.82
Female	107 (12.9)	13 (12.14)	0.933 (0.50–1.73)	
Genotype				
3	459 (55.4)	52 (11.4)	Ref.	0.27
1	344 (41.5)	48 (14)	1.26 (0.83–1.92)	
Viral load				
$<8 \times 10^5$	357 (43.1)	45 (42.05)	Ref.	0.74
$\geq 8 \times 10^5$	422 (51)	52 (48.59)	0.93(0.60–1.42)	

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.

than 0.5% to 2%, encompassing approximately 1.5 million individuals living with this virus.[24] The distribution of HCV genotypes varies geographically and among different populations.[25] Based on studies conducted in various regions of Iran, Genotypes 1a and 3a have the highest prevalence in the country.[26,27] The availability of DAA therapies has revolutionized the treatment of HCV, achieving cure rates exceeding 95% in the majority of cases.[24] However, the selection of a DAA regimen might vary depending on the HCV genotype.[28] The genetic diversity of HCV genotypes has posed a significant challenge for vaccine development and drug advancements. Consequently, determining the HCV genotype is an essential tool for identifying the appropriate treatment regimen and predicting treatment outcomes. In the present study, we delved into the examination of these variables.

The results of the present study revealed that Genotype 3 (55.4%) were the most common genotype, followed by Genotype 1 (41.5%). Genotype 3 was predominant in all age groups. Genotype 1 exhibited a higher frequency following genotype 3. Genotypes 2 and 4 were rare genotypes in our study region. In Genotype 3, subtype 3a with a frequency of 55.7% was the most common subgroup, followed by 1a with 34.3% frequency. These findings were consistent with the results reported by Zarkesh-Esfahani et al.[26] and Hadinedoushan et al.[25] in Iran. Their findings demonstrated that the most common genotypes were 3a, 1a, and 1b in descending order. The results of a study on patients with chronic HCV infection,[29] a study by Davarpanah et al., and a study by Hajia et al,[30] who classified subgroup 1a as the predominant genotype, were different from the findings of the present study.

TABLE 4 Comparison of viral load by demographic and clinical characteristics.

Variable	Viral load median (IQR)	*p*-Value
Age group		
<39	825,965 (3,300,255)	0.02
40–59	1,296,000 (4,016,605)	
≥60	656,177.5 (2,605,528)	
Sex		
Male	1,104,790 (3,904,480)	0.004
Female	525,000 (2,498,093)	
Cirrhosis		
Yes	910,320 (2,949,920)	0.71
No	993,500 (3,593,180)	
Fatty liver		
Yes	1,204,225 (4,734,982.5)	0.46
No	939,070 (3,074,610)	
Genotypes		
3	886,000 (297,5310)	0.02
1	1270,000 (4,663,296.5)	

Abbreviation: IQR: interquartile range.

A study conducted in 2017 demonstrated that the prevalence of hepatitis C genotypes has changed over time. This study showed that Genotype 1 was more common in the 1990s and early 2000s, but its prevalence has decreased since then, while Genotype 3 has become more prevalent in recent years.[31] Additionally, a study by Sefidi et al.[32] in 2013 indicated that the frequency of genotypes is changing over time, favoring an increase in Genotype 3 with a higher frequency of 3a. Possible changes in factors such as the mode of infection transmission, changes in public health status, and varying lifestyles across different geographic regions can contribute to such shifts in genotype distribution. It is thought that Genotypes 3a and 1a are prevalent among HCV-infected patients due to intravenous drug misuse.[33] The high prevalence of Genotype 3a in western Iran might be attributed to the widespread intravenous drug use in this area.[34] According to some research, intravenous drug use is a major risk factor for HCV transmission, often associated with acquiring Genotype 3.[35] In contrast, Genotype 1 is commonly associated with blood transfusions and medical procedures.[36]

A study conducted on predominant genotypes in neighboring countries of Iran showed that Genotype 4 was the main genotype in Yemen, Kuwait, Iraq, and Saudi Arabia. However, Genotype 1b was more prevalent at the western border of Iran (Turkey) and Genotype 3a was more common at the eastern border of Iran with Pakistan. Factors such as differences in ethnicity, transmission routes, and socioeconomic factors can explain the varying pattern of HCV genotypes in the present study compared to neighboring countries.[25]

Considering that Genotype 3 requires a shorter treatment duration compared with other genotypes, leading to reduced costs and side effects, the high frequency of Genotype 3 HCV among infected patients in the present study holds promising prospects for treatment and controlling HCV infection. Some authors argue that concurrent infection with different types of HCV, even in high-risk groups, is very rare.[37] In the present study, only 0.8% of patients were infected with two different genotypes.

In the present study, the mean age of the participants was 40.38 years, ranging between 11 and 80 years. The age range with the highest number of participants was 20–39 years, which might indicate the presence of risky behaviors within this age range. Given the small number of individuals under 20 years of age, they were grouped in the first category, in the age group 20–39 years. It was also observed that individuals aged 40–59 years had a higher prevalence of detectable viral load, which aligns with findings from several studies suggesting the effect of age on the viral load.[38,39] Furthermore, in the present study, the prevalence of the disease was 12.9% in women compared to 87.1% in men. Our results support the findings of a study by Meda et al.,[40] indicating a higher seroprevalence of HCV in men (3.9%) compared to women (3.2%). This difference could be attributed to differences in the health-seeking behaviors of women compared to men.[40]

No significant relationship was found between cirrhosis and viral load as well as fatty liver and viral load in our study. This finding is inconsistent with previous studies that considered high viral load as a risk factor for the progression of Hepatitis C to cirrhosis and hepatocellular carcinoma.[1,41]

Pandey et al.[6] found that genotype 3a was responsible for liver disease in HCV-positive individuals. Additionally, Chakravarti et al.[42] suggested Genotype 1 as a potential factor for the severity of liver disease. In the present study, no significant correlation was detected between genotypes and liver conditions such as fatty liver and cirrhosis, which is contrast to the results of the two studies.[6,42] Hence, our study does not support the notion of a specific HCV genotype having a pronounced impact on the severity and outcome of chronic liver disease.

On the other hand, hepatitis C is considered an emerging infectious disease in Iran, especially among injection drug users, and a substantial amount of time is required before witnessing its consequences such as cirrhosis and hepatocellular carcinoma among this population. This might explain the lack of anycorrelation between genotypes (especially Genotype 3) and liver diseases in the present study. Our findings demonstrated no significant relationship between the occurrence of liver conditions, including cirrhosis and fatty liver, and gender, which contradicts the results obtained from the study by Yelemkoure et al., where men were found to be at increased risk of liver cancer or cirrhosis following chronic HCV infection.[1]

Considering that Genotypes 2 and 4 were rare with fewer than five cases, only Genotypes 1 and 3 were included in the analysis of variables. The relationship between HCV genotype and viral load has been extensively evaluated in various studies with conflicting results. Some studies have reported a significant association, while others have described it as insignificant. In the present study, viral load was significantly higher in Genotype 1 compared with Genotype 3 (the

likelihood of high viral load was 32% higher in Genotype 1 compared to Genotype 3). Additionally, the data indicated that Genotype 1 (58.5%) involved a higher number of patients with high viral load, which contradicts the findings of a study by Kaur et al.[43] Due to the high replication rate of Genotype 1, which is believed to be an evasion mechanism from the host immune system compared to other genotypes, a higher viral load is expected in this genotype. However, these findings are contradictory to the results of several studies.[4,38] The results of the present study were in line with those reported by Chakravarti et al.[42] There was a significant association between viral load and gender in our study. High viral load was observed more frequently in males compared to females in the present study, which is inconsistent with the findings of a study by Audu et al.[38] This could be attributed to increased sensitivity, screening, and treatment in females compared to males.

Furthermore, despite the fact that the Chance of Genotype 1 was 16% higher in females compared to males in the present study, no significant difference was observed between HCV Genotypes 3 and 1 in terms of gender. Our results corroborated similar reports.[25] As a result, HCV Genotype 3, the predominant genotype in Western Iran, exhibits the highest prevalence among males, and Genotype 2 indicates the second highest frequency among HCV patients in the western region of the country. Additionally, Genotype 1 has the highest frequency in the age group 20–39 years. Given the high prevalence of Genotype 3 hepatitis C in Kermanshah province, it is advisable to prioritize the provision of DAA drugs with pangenotypic effects such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir.

5 | LIMITATIONS

Due to the incomplete access to patients' demographic information, other confounding factors may have influenced cirrhosis, fatty liver, and viral load, such as alcohol consumption or coexisting illnesses and their impact on liver damage, or prior treatment of patients before entering the study, which could have affected the viral load. Additionally, addiction, which is a major factor in HCV infection, was not fully recorded, making it challenging to confidently assert the relationship between injection addiction and Genotype 3.

AUTHOR CONTRIBUTIONS

Babak Sayad: Investigation; project administration; supervision; visualization; writing—review and editing. **Arezoo Bozorgomid**: Investigation; supervision; writing—review and editing. **Nazanin Sayad**: Data curation; writing—review and editing. **Marya Azhdari**: Data curation. **Maryam Bahadori**: Data curation. **Shahab Rezaeian**: Formal analysis. **Maryam Gholizadeh**: Data curation; writing—original draft.

ACKNOWLEDGMENTS

We also like to acknowledge the cooperation of Vice Chancellor for Research of Kermanshah University of Medical Sciences. This study was supported by a grant from the Vice Chancellery for Research and Technology, Kermanshah University of Medical Sciences (grant number: 4030195).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. The data is confidential and is in the personal folder of the project manager and will be emailed if needed.

ETHICS STATEMENT

The protocol was approved by the Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS. REC.1402.018). Informed consent was obtained from all subjects involved in the study.

TRANSPARENCY STATEMENT

The lead author Maryam Gholizadeh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Sayad B, Bozorgomid A, Sayad N, et al. The prevalence of hepatitis C virus genotypes and factors associated with cirrhosis, fatty liver, and viral load: a registry-based cross-sectional cohort study in Western Iran during 1999–2023. *Health Sci Rep*. 2024;7:e70079. doi:10.1002/hsr2.70079